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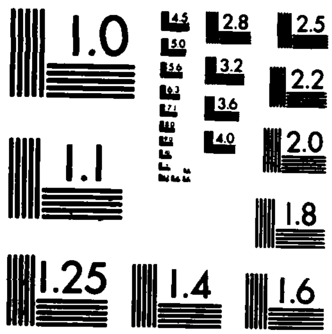

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Voltammetric Studies of Zomepirac Sodium and Its Determination in Tablets by Differential-Pulse Polarography

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VOLTAMMETRIC STUDIES OF ZOMEPIRAC SODIUM AND ITS DETERMINATION IN TABLETS BY DIFFERENTIAL-PULSE POLAROGRAPHY

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ABSTRACT

A simple differential-pulse polarographic method has been developed for the determination of Zomepirac Sodium in tablets. Britton-Robinson buffer pH 11.0 containing 5% v/v of methanol was employed as the supporting electrolyte. The E_p occurs at -1.50 volts. Results obtained by the proposed method are in excellent agreement with those provided by both the official and the manufacturer's methods of assay. Commonly used tablet excipients were found not to interfere in the analyses.

Keywords: Zomepirac Sodium determinations; differential-pulse polarography; controlled potential coulometry; cyclic voltammetry

Zomepirac sodium (sodium salt of 5-(4-chlorobenzoyl)1,4-dimethyl pyrrol-2-yl acetic acid) is a non-steroidal anti-inflammatory agent approved exclusively as an analgesic in the treatment of mild and moderately severe pain[1] and is formulated as a 100 mg tablet.

The official method of analysis in the United States Pharmacopeia[2] involves three extraction and two centrifugation steps prior to the final U.V. spectrophotometric analysis at 329 nm. The method is tedious and requires very careful sample handling which is not usually amenable to routine analysis. The manufacturer's[3] method of assay is similar to that of the U.S.P.[2].

Other methods of assay include H.P.L.C. for the determination of the drug in blood plasma[4] and in purity and stability tests[5]. In addition, a nonaqueous titrimetric method is employed by the U.S.P.[2] for the determination of Zomepirac sodium as the raw material. Thin-layer chromatography[2] and radioimmunoassay[6] are other methods reported for the analysis of this substance.

In this report, differential-pulse polargraphy has been applied to the determination of Zomepirac sodium and involves the reduction of the conjugated carbonyl group of the benzoyl substituent. Only a single extraction is required prior to the polarographic analysis and none of the excipients present in the tablet interfere with the analysis. The d.p.p. peak height varies linearly with the concentration of the drug over the range of 1×10^{-5} to 5×10^{-4} M/l. The method is accurate, sensitive and easy to apply for routine analysis.

EXPERIMENTAL

Apparatus and Conditions for Polarographic Analysis

A Fisher, Model 320, pH meter fitted with a glass-calomel electrode system was employed to measure the pH values of the solutions.

A PAR, Model 174, polargraph equipped with a drop timer (Model 172A) and a Houston Omnigraphic Model 2000 recorder were used in the investigations. A three-electrode combination was employed which consisted of a saturated calomel electrode, a dropping-mercury electrode and a platinum wire as the auxiliary electrode. A conventional H-type cell was maintained at 25 ± 1°C and all sweeps utilized a scan rate of 2 mV s^{-1} and a drop time of 2 s.

In Britton-Robinson buffer (pH 11.0) the instrumental parameters were: applied potential range -1.0 to -2.5 V; current 50 μA full scale; height of mercury column 75 cm; flow rate of mercury 1.265 mg s^{-1}; modulation amplitude, set at 50 mV; and low pass filter, set at a time constant of 1 s. The instrument was operated in the differential-pulse mode.

Controlled-potential Coulometry

A PAR, Model 173, potentiostat-galvanostat, equipped with a PAR, Model 377A, three compartment coulometric cell system was connected to a Hi-Tek digital integrator and digital voltmeter.

Nineteen ml of Britton-Robinson buffer, pH 11.0, were placed in the coulometric cell on top of a 5-ml layer of triple distilled mercury and 1 ml of 10^{-2} M solution of Zomepirac sodium in methanol was added. The system was purged for 10 min with purified nitrogen. The applied potential

was set at -1.8 V with a current range of 10 μA full scale and the solution was electrolyzed until the digital readout indicated a constant but small count. One hour was required to complete the electrolysis. The process was repeated with a blank consisting of 19 ml of Britton-Robinson buffer and 1 ml of methanol.

Cyclic Voltammetry

Cyclic voltammetric experiments at a hanging mercury drop electrode were performed with a four-component system consisting of a PAR EG & G, Model 175, Universal Programmer, a PAR, Model 173, potentiostat-galvanostat, a Houston Model 2000 Omnigraphic recorder and a PAR, Model 9323, hanging mercury drop electrode fitted with a polarographic cell.

Two supporting electrolyte systems were employed. In Britton-Robinson buffer, pH 11.0, the parameters were: potential range, -1.1 to -1.65 V; current range, 10 μA; scan rate varied from 10 mV s^{-1} to 200 mV s^{-1}.

In a dimethylformamide/lithium perchlorate system, the settings were: potential range, -0.4 to -2.2 V; current range and scan rates were the same as in the previous system.

Reagents

The following reagents were used, all of analytical-reagent grade: barbital, boric acid, citric acid, lithium perchlorate, potassium hydrogen phosphate, dimethylformamide, anhydrous methanol, 0.2 N sodium hydroxide, and 1% lithium perchlorate in DMF. Britton-Robinson buffers were prepared with distilled, deionized water at intervals of 0.2-0.3 pH unit over the pH range of 6.0-11.0.

Reference Standard

Zomepirac sodium (99.44%) was obtained from McNeil Laboratories, Canada, Ltd. and used without further purification.

pH Dependence Studies

These studies were carried out in Britton-Robinson buffer over the pH range 6.0 to 11.0

Preparation of Calibration Graphs

A stock solution of zomepirac sodium (10^{-2}M) was prepared in anhydrous methanol. Five test solutions of varying concentrations, 1 to 5 x 10^{-4} M were prepared by appropriately diluting the stock solution with Britton-Robinson buffer, pH 11.0. In the total sample volume of exactly 20 ml, the amount of methanol was always maintained at 1 ml.

All samples were purged with oxygen-free nitrogen for 10 min prior to each run and a stream of nitrogen was allowed to flow gently over the surface of the solution during the electroreduction. Samples of each of five concentrations were run five times and resulted in a correlation coefficient for the graph of 0.9992.

Diffusion Dependence Studies

These studies were carried out at pH 11.0 on a 5 x 10^{-4} M solution of zomepirac sodium. The applied potential was from -1.0 to -2.5 V and the height of the mercury column ranged from 60 to 80 cm. The weight of mercury was also obtained at each of five heights over that range.

Analysis of Pharmaceutical Dosage Form

Only one dosage form, 100 mg tablets, was available from the manufacturer.

Twenty tablets were weighed, finely powdered and an amount of powder corresponding to the weight of one tablet was accurately weighed into a 100 ml beaker. Twenty ml of methanol were added and the sample stirred magnetically for 15 min. The mixture was transferred quantitatively into a 50 ml volumetric flask, diluted to volume with methanol and then filtered through Whatman No. 1 paper discarding the first 5 ml of the filtrate. One ml of the filtrate was transferred to the polarographic cell and 19 ml of Britton-Robinson buffer, pH 11.0, were added. As previously described, the solution was purged for 10 min with nitrogen prior to recording the polarogram.

The amount of Zomepirac sodium in the form of the free acid was computed by the direct comparison method, using a reference standard solution of Zomepirac sodium (0.7649×10^{-2} M/l).

Content Uniformity Test

Ten tablets were randomly selected from the sample. Each tablet was placed in an individual 150 ml beaker, 20 ml of methanol were added and the system was allowed to stand for 5 min in order to promote disintegration of the tablets. The remaining larger lumps of tablet mass were crushed with a glass rod and the mixture stirred magnetically for 20 min. After transferring the mixture quantitatively to a 50 ml volummetric flask, the determination was continued as described in the previous section.

Macroscale Electrolysis

The procedure used was similar to that for the controlled potential coulometry except the cell contained 200 mg of Zomepirac sodium in 25 ml of 20% v/v methanol in 1 N NaCl. The pH was adjusted to 11.0 with NaOH solution. The applied potential remained at -1.8 V while the reduction time was 8 hr. The initial yellow colour of the solution turned colourless upon completion of the reduction and then the product together with the supporting electrolyte was separated from the mercury and freeze-dried.

Results and Discussions

Zomepirac sodium exhibits three d.c. and d.p. polarographic waves in Britton-Robinson buffer over the pH range 6.0 to 11.0 (Fig. 1 and 2). At pH 6.0, a single well-resolved wave is observed with an $E_{1/2}$ value of -1.28 V. This wave is pH sensitive and the $E_{1/2}$ moves cathodically with increasing pH. The second wave appears at more negative potentials within the pH range of 6.8 to 10.0 as illustrated by B in Fig. 1. The $E_{1/2}$ value of this wave occurs at -1.45 V and is independent of pH. At pH 11.0, the two waves shown in B merge to form one wave, C, with an $E_{1/2}$ value at -1.5 V. This latter wave is well-resolved, intense and is suitable for quantitative work. The corresponding differential pulse waves are presented in Fig. 2.

For reasons which will be discussed in detail, wave A is attributed to the reduction of the keto group of the benzoyl substituent by a one-electron process to give a free radical anion. In acidic medium the radical anion becomes protonated to give a free radical which undergoes

dimerisation to the pinacol. At higher pH's, the radical anion undergoes a further one electron reduction to the dianion which subsequently becomes protonated to give the alcohol. This second reduction is exhibited by the second wave in B.

The graph of diffusion current versus the square root of the corrected height of mercury column is a straight line with slope 0.1818 $\mu A\ cm^{-1/2}$ nd does not pass through the origin. Only one reduction peak was observ in the cyclic voltammetric experiment in Britton-Robinson buffer pH .0 (Fig. 3) where the E_p occurred at -1.53 V. No reverse anodic peak observed under the sweep rate range studied. Detailed analysis of the cathodic peak indicated a peak potential shift of 40 to 50 mV as the sweep rate $\bar{\nu}$ was varied from 200 mV s^{-1} to 10 mV s^{-1}. The peak current varied linearly with the square root of scan rate over this range indicating the absence of any complicating homogenous reaction on the time scale of the experiment[7]. A plot of $i/\bar{\nu}^{1/2}$ vs $\bar{\nu}$ is independent of scan rate implying a predominantly diffusion controlled process.

The cyclic voltammogram of Zomepirac sodium in DMF/$LiClO_4$ shows three cathodic peaks and one reverse anodic peak. The E_{Pc} waves occurred at -1.75 V, -1.85 V and -2.08 V. The height of the peak at -2.08 V was twice that of either of the first two peaks. The E_{Pa} was at -1.98 V (Fig. 4).

The coulometric analysis of Zomepirac sodium indicated that two electrons per molecule were involved in the electroreduction process.

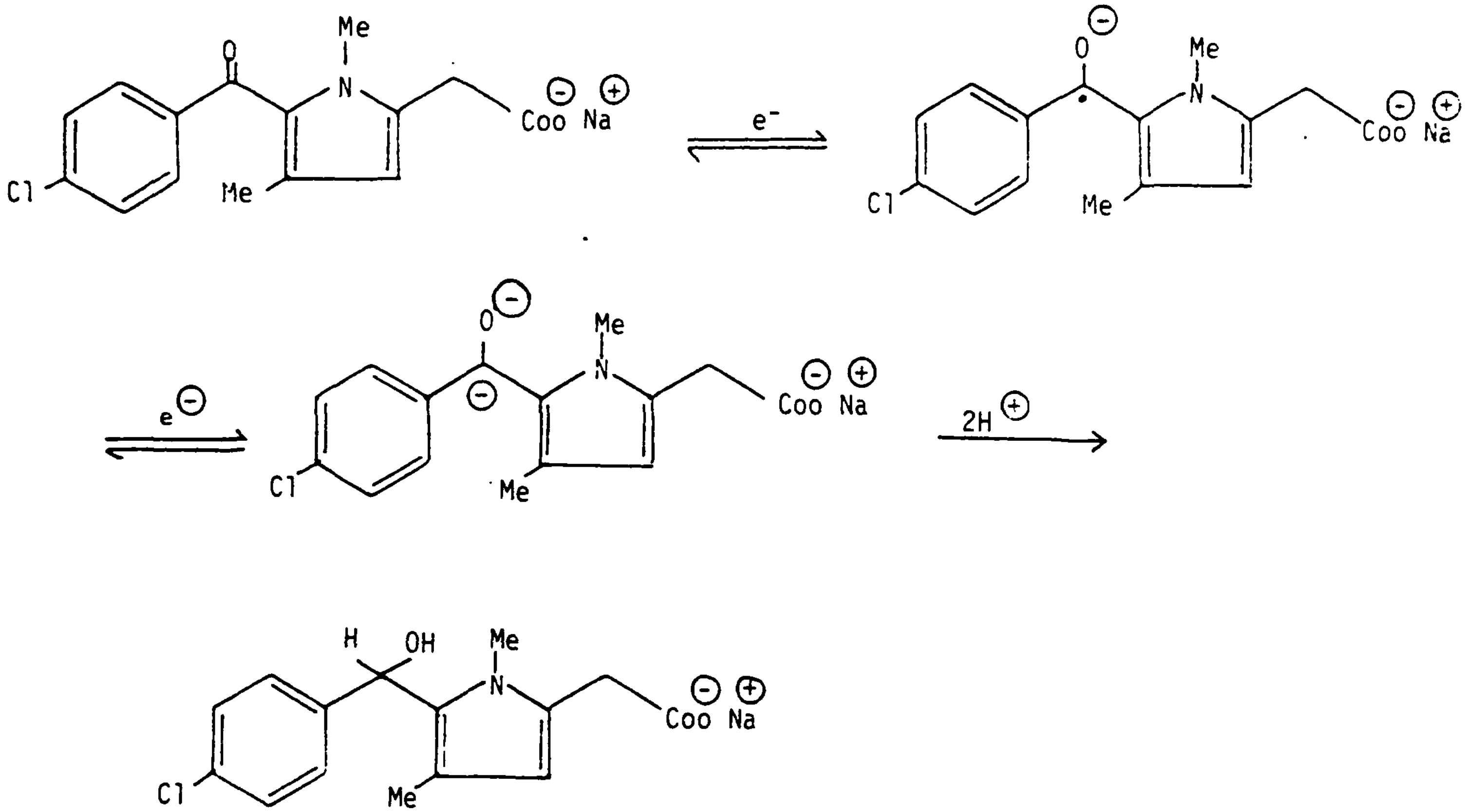
The UV absorption spectra of Zomepirac sodium in alkaline media shows two maxima. The first exhibited a λmax at 260 nm and a log ε = 3.94 while the λmax of the second was at 328 nm and the log ε = 4.04. The reduced product shows only one maximum at 228 nm with a log ε = 3.97. Concentration of the reduced product was based on the initial concentration

of Zomepirac sodium taken. The reduced product is unstable in acid and decomposes rapidly to give a reddish-pink precipitate.

IR and NMR spectra were obtained on samples of the freeze dried product from the macroscale electrolysis. In acetone d_6-D_2O, Zomepirac sodium exhibits five peaks on the NMR (60 mHz) with delta values at ∂ 1.6 (S 3H), 3.4 (S 2H), 3.55 (S 3H), 5.9 (S 1H) and 7.3 (quartet 4H). In the same solvent the reduced product exhibits six peaks on the NMR (200 mHz) with delta values at ∂ 2.5 (S 3H), 3.8 (S 3H), 3.95 (d 2H), 6.3 (S 1H), 6.6 (S 1H) and 7.95 (b 4H).

The IR (KBr) spectra of the reduced product of Zomepirac sodium shows an absence of the carbonyl peak at about 1660 - 1690 nm which is present in the IR spectra of Zomepirac sodium itself. The absence of the carbonyl group in the reduced product is also indicated by the disappearance of a UV absorption peak in the range 250 - 350 nm. The NMR peak at ∂ 6.6 owing to a single proton observed for the product confirms that the carbonyl group is the site of the electroreduction process.

From the results obtained, we propose the following pathway for the reduction:



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H
OH
Me
N
Coo Na
Cl
Me

The polarogram of deschlorozomepirac sodium was identical to that for the parent Zomepirac which indicates that the p-chloro atom does not participate in the electroreduction.

Table I gives the results of the assay of Zomepirac sodium tablets based on the average value obtained with a sample of twenty tablets. The standard deviations of the method together with the analysis obtained by the manufacturer's quality control laboratory are presented for comparative purposes. The assay provides results that are equally comparable to those of the manufacturer, at both pH values of 11.0 and 6.0.

Although the d.c. wave could have been used for analytical purposes, the differential-pulse wave is much better resolved, as illustrated in Figures 1 and 2. The proposed method has the advantage of simplicity, high sensitivity and rapidity. It has the same disadvantage as the official spectrophotometric method, however, in that certain degradation products, if present, might not be detected.

In Table II, the average of the results obtained with ten individual tablets is presented.

Table I - Analysis of Zomepirac Sodium Tablets at two pH values

Labelled Claim 100 mg	Differential-Pulse Method		Manufacturers UV Method
	pH 6.0	pH 11.0	
Amount found (%)	96.6 ± 0.2	98.7 ± 0.4	97.54

Table II - Average Value for the Analysis of Single Zomepirac Tablets at pH 11.0

Labelled Claim 100 mg	Differential-Pulse Polarographic Method pH 11.0	Manufacturers UV Method
Average mg/tab found	100.7 ± 1.0	99.15

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FIGURE LEGENDS

Figure 1. Effect of pH on the sampled d.c. polarographic waves of zomepirac sodium (5×10^{-4} M) in Britton-Robinson buffer. Curve A, pH 6.0; Curve B, pH 8.0; Curve C, pH 11.0

Figure 2. Effect of pH on the d.p. polarographic waves of zomepirac sodium (5×10^{-4} M) in Britton-Robinson buffer. Curve A, pH 6.0; Curve B, pH 8.0; Curve C, pH 11.0

Figure 3. Cyclic voltammogram of zomepirac sodium (5×10^{-4} M) in Britton-Robinson buffer, pH 11.0

Figure 4. Figure 4. Cyclic voltammogram of zomepirac sodium (5×10^{-4} M) in DMF/$LiClO_4$

FIG 1

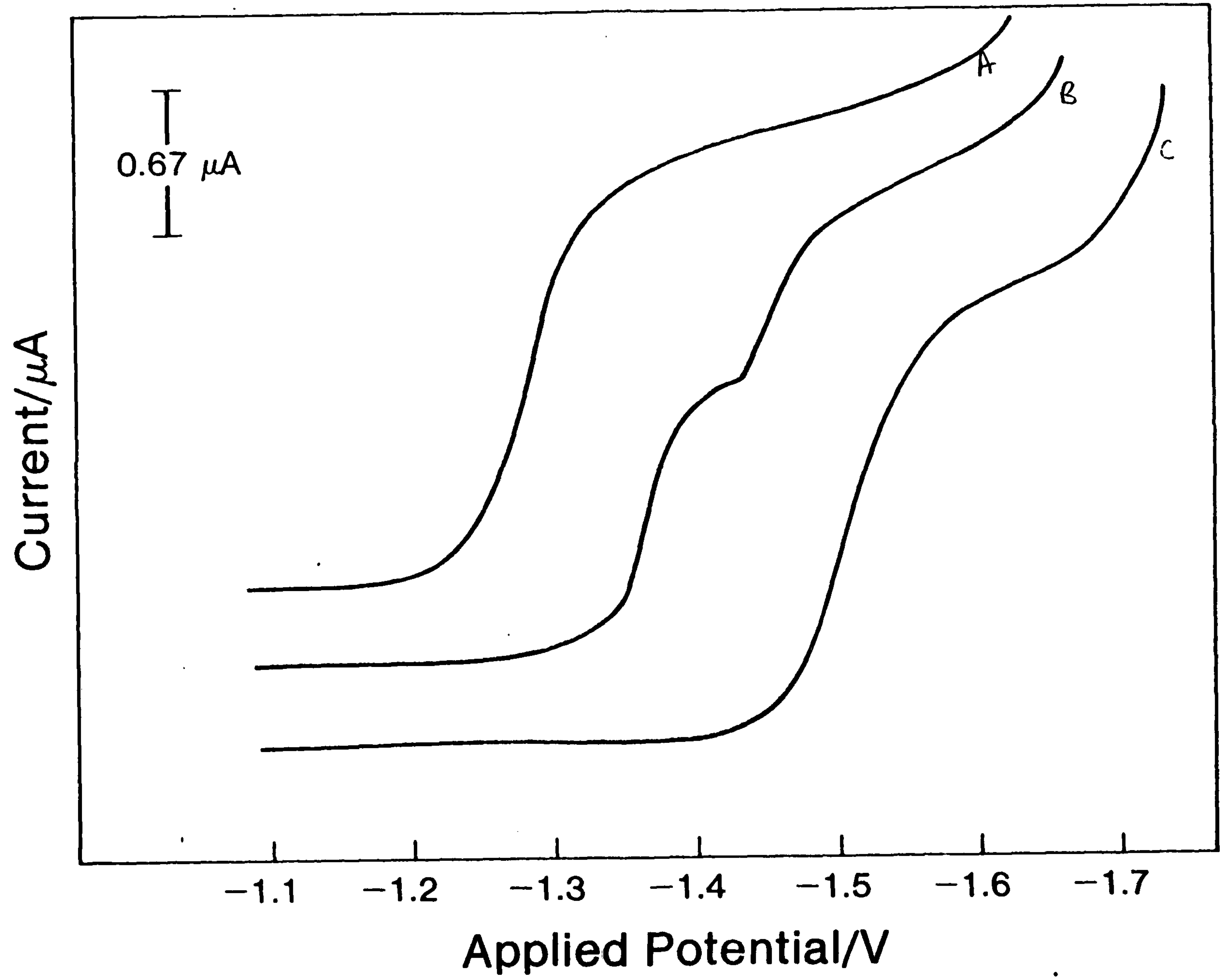


FIG 2

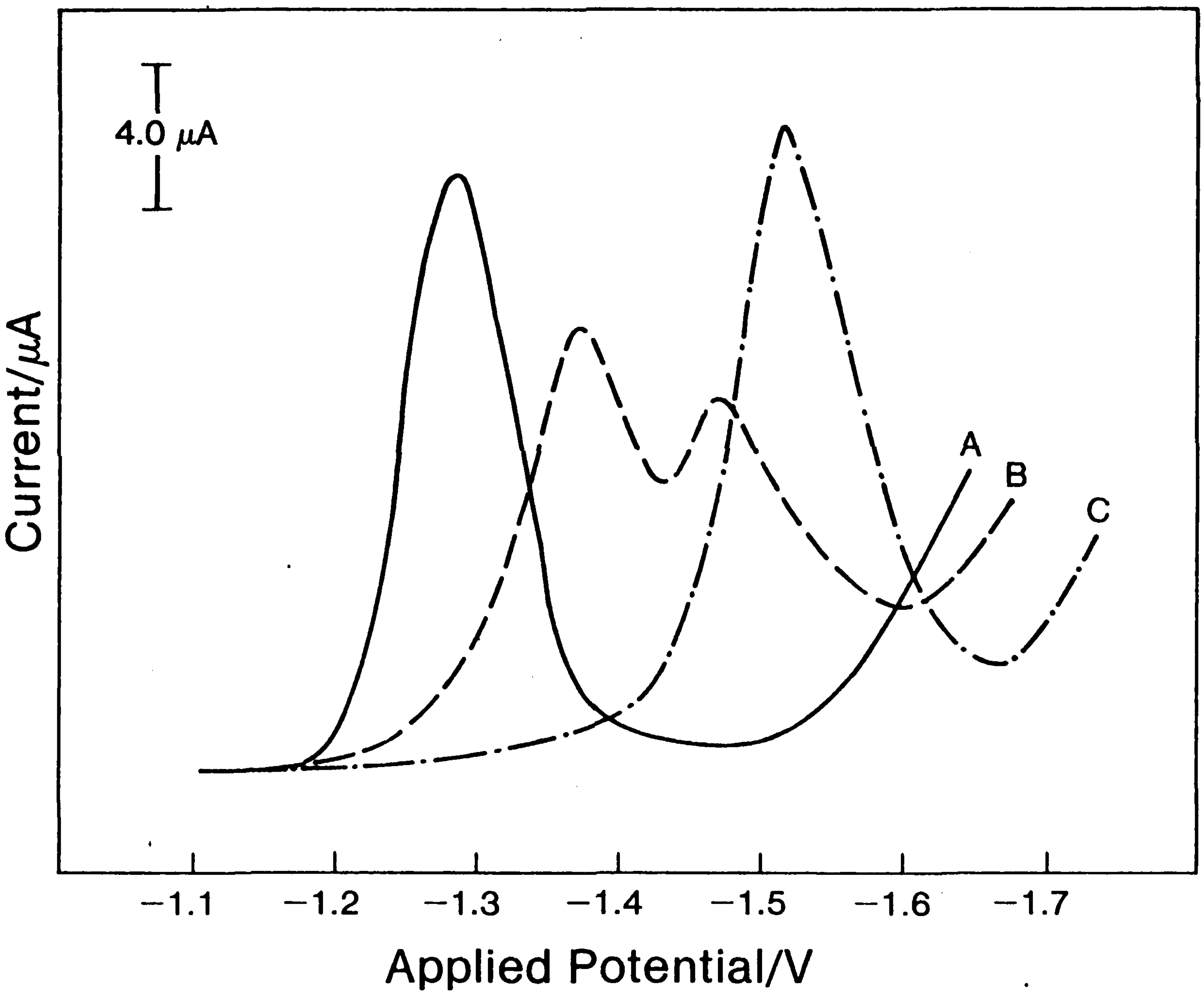


FIG 3

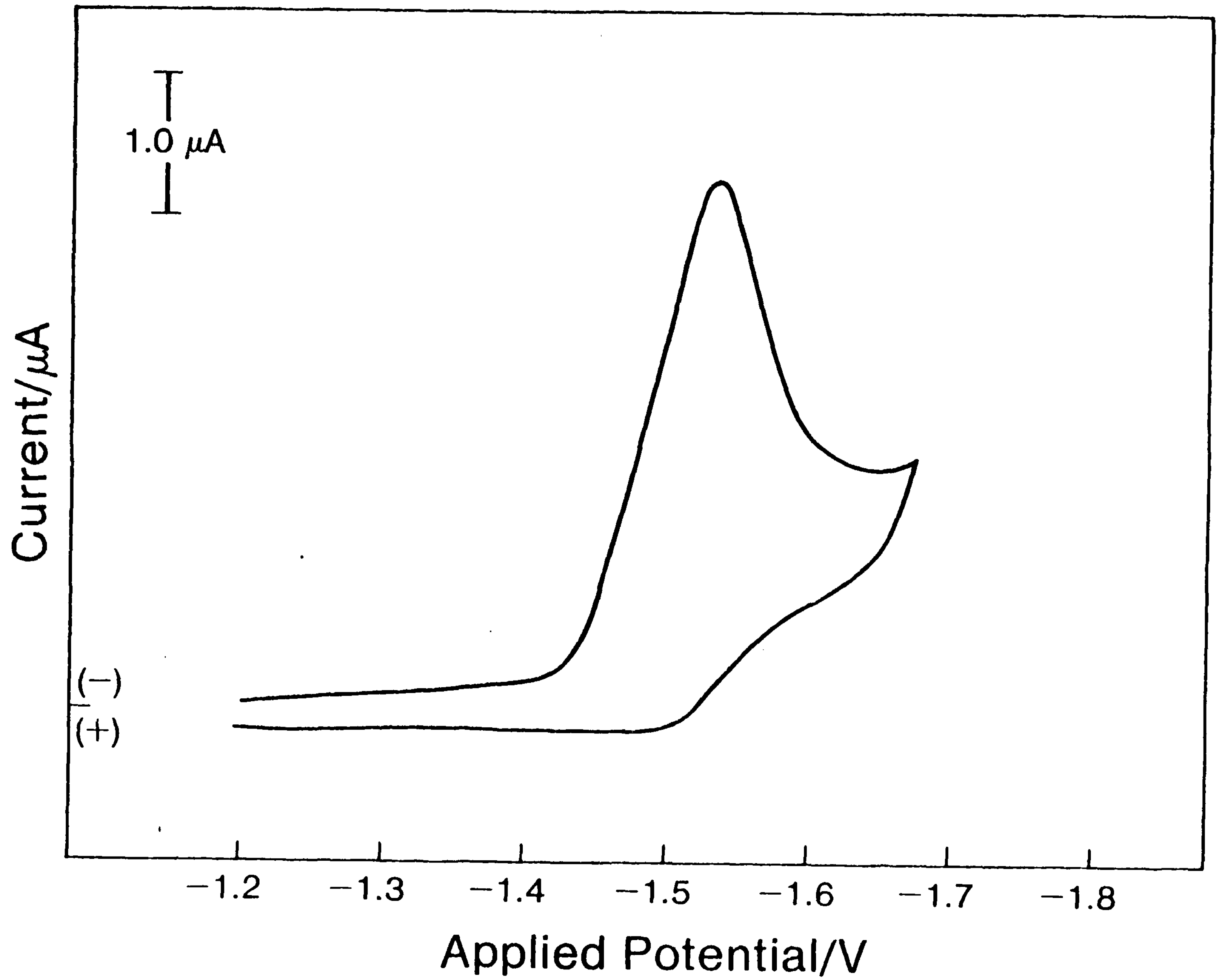
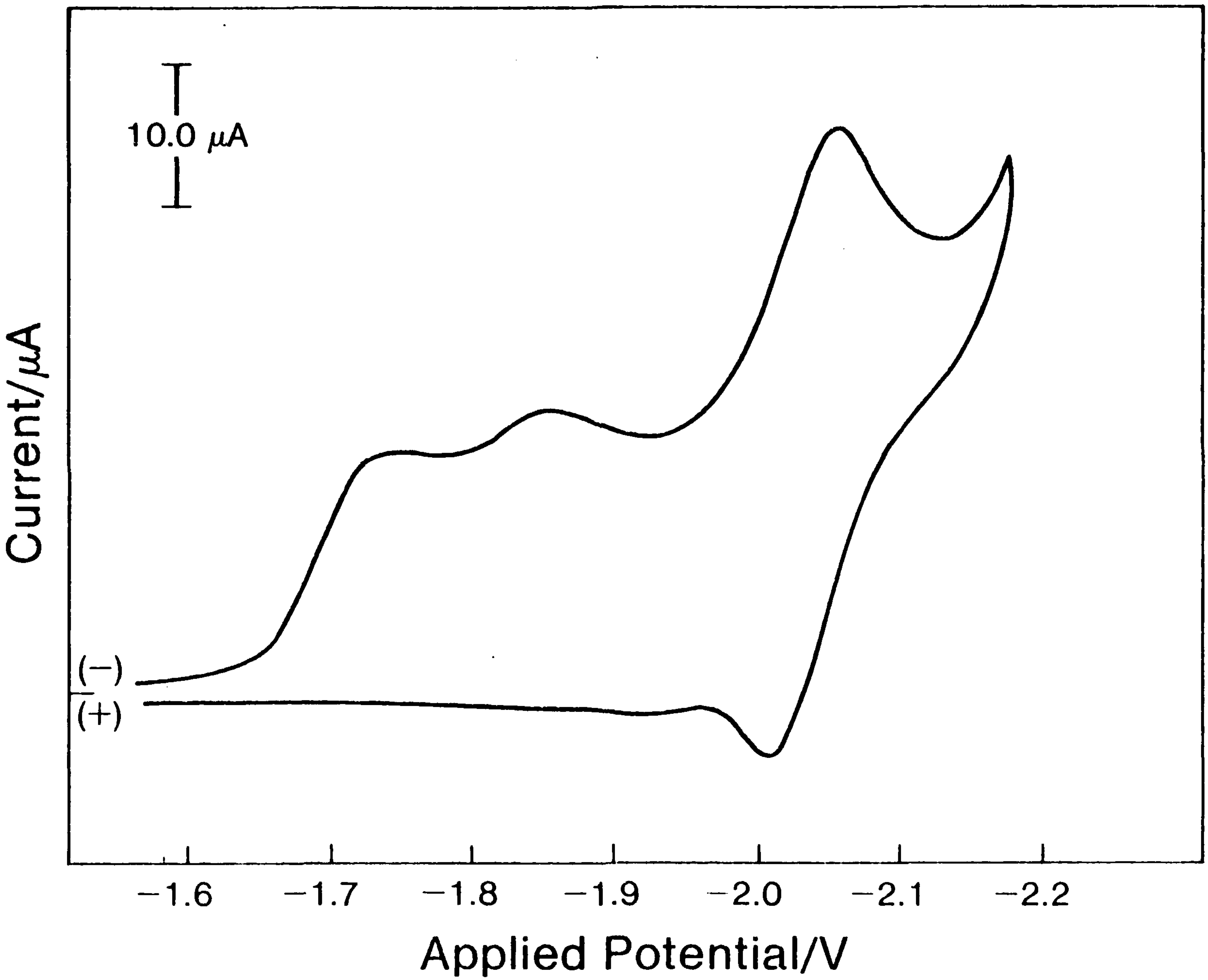


FIG 4



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